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Intranasal lidocaine and midazolam for procedural sedation in children

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ABSTRACT

Objective To evaluate the safety and efficacy of a sedation protocol based on intranasal lidocaine spray and midazolam (INM) in children who are anxious and uncooperative when undergoing minor painful or diagnostic procedures, such as peripheral line insertion, venipuncture, intramuscular injection, echocardiogram, CT scan, audiometry testing and dental examination and extractions.

Patients and design 46 children, aged 5–50 months, received INM (0.5 mg/kg) via a mucosal atomiser device. To avoid any nasal discomfort a puff of lidocaine spray (10 mg/puff) was administered before INM. The child's degree of sedation was scored using a modified Ramsay sedation scale. A questionnaire was designed to evaluate the parents' and doctors' opinions on the efficacy of the sedation. Statistical analysis was used to compare sedation times with children's age and weight.

Results The degree of sedation achieved by INM enabled all procedures to be completed without additional drugs. Premedication with lidocaine spray prevented any nasal discomfort related to the INM. The mean duration of sedation was 23.1 min. The depth of sedation was 1 on the modified Ramsay scale. The questionnaire revealed high levels of satisfaction by both doctors and parents. Sedation start and end times were significantly correlated with age only. No side effects were recorded in the cohort of children studied.

Conclusions This study has shown that the combined use of lidocaine spray and atomised INM appears to be a safe and effective method to achieve short-term sedation in children to facilitate medical care and procedures.

What is already known on this topic

- Intranasal midazolam is used as a sedative agent in children undergoing minor painful or diagnostic procedures.
- In about 65% of cases midazolam produces nasal burning and irritation making nasal administration painful for children.

What this study adds

The use of lidocaine spray before intranasal administration of midazolam prevents nasal discomfort and facilitates minor painful and diagnostic procedures in anxious and uncooperative children without any significant side effects.

INTRODUCTION

A non-invasive route of drug administration may be useful to obtain short-term sedation for diagnostic and painful procedures in uncooperative children.Midazolam is a water-soluble benzodiazepine with rapid onset and short duration of action.[1] Intranasal midazolam (INM) has been found to be effective in doses ranging from 0.2 to 0.5 mg/kg when used for conscious sedation.[2–3] The intranasal route is preferable since it obviates the need for intravenous access and is easily accessible.[4–5] Previous studies have shown that therapeutic levels of midazolam in the cerebrospinal fluid indicate a more rapid rate of absorption via intranasal administration compared to the oral route, due to the rich vascular plexus cavity that communicates with the subarachnoid space via the olfactory nerve.[6–7]

INM has been used successfully in a variety of paediatric clinical situations, such as laceration repair,[8] dental extractions,[9] ophthalmological tests,[10] burn patients[11] and venepuncture.[12] Although most studies investigating INM administered the drug by drop instillation, new methods such as the use of spray devices are being explored. Atomisation devices were assessed in several studies and showed tolerance, safety and efficacy.[13] A mucosal atomiser device (MAD) delivers medications via a fine spray over a broad surface area in the nasal cavity. It also reduces sneezing and coughing compared to other devices which sometimes need a larger dose of drug to produce sedation, as previously reported both in an experimental animal model and in patients with difficult intubation.[14–15]

Several studies revealed that INM administered by MAD or by drops resulted in nasal burning and a bitter taste in up to 66% of patients, making the experience unpleasant and the procedure more difficult to complete.[16–17]

The administration of intranasal lidocaine prior to the use of INM has been reported to be beneficial in reducing the burning sensation from INM.[18] This may be due to a sharp activation of the sympathoadrenal system resulting in topical nasal anaesthesia with subsequent reduction in nasal discomfort.[19]

In this study we prospectively evaluated the safety and efficacy of a simple sedation protocol based on INM administered by MAD in association with lidocaine spray to avoid any nasal discomfort related to INM, in children undergoing minor painful and diagnostic procedures.

MATERIALS AND METHODS

We performed a prospective observational clinical study to evaluate the safety and efficacy of INM administration via MAD preceded by one spray of lidocaine to both nostrils in children aged 5–50 months, admitted to hospital or referred to the emergency department. Parents were provided with information about the trial before delivery of the puffs. The lidocaine used in this study was Ecocain 10 g/100 ml spray (Molteni Dental, Scandicci, Italy) without gas propellants and one puff provided a dose of 10 mg. In order to make the puff more acceptable and avoid frightening the children, the physicians instructed mothers who then administered the lidocaine spray. A 5 mg/ml solution of midazolam (Midazolam-Hameln 5 mg/ml; Hameln Pharmaceutical, Hameln, Germany) was administered 60 s later by a physician in both nostrils at a dose of 0.5 mg/kg (maximum dose 10 mg=2 ml) using a 2.5 ml syringe connected to a MAD (Wolfe Tory Medical, Salt Lake City, Utah, USA) (figure 1).

This study was conducted in children who did not have an intravenous access device, and were uncooperative or anxious before a specific procedure such as venipuncture, peripheral line insertion, intramuscular injection, echocardiogram (ECHO) examination, CT scan, audiometry and dental extractions. Children were not required to be fasting prior to the administration of INM. Children were excluded if they had an ASA classification of III or higher, a known allergy to benzodiazepines, an upper respiratory tract infection with nasal discharge, a known liver disease or respiratory distress.

Prior to drug administration, all children were weighed and baseline blood pressure and heart rate were measured. Blood pressure measurement was recorded at 5 min intervals. Pulse oximetry was continuously monitored and the lowest oxygen saturation (O_2sat) was recorded; hypoxemia was considered mild when O_2sat was between 91% and 95%, moderate when between 75% and 90% and severe when below 75%. 'Start time' was defined as the time of sedation onset following INM administration and fixed as the moment when the patient presented a sluggish response to a light glabellar tap. 'End time' was defined as the end of the sedation effect, determined when the patient spontaneously returned to baseline consciousness. The duration of sedation was calculated as the difference between the end and start times. The child's degree of sedation and reactivity during the procedures were scored using a modified Ramsay sedation scale and a reactivity score (table 1).[20] A sedation score of 1 and a reactivity score of 3 were considered acceptable. A visual analogue scale (VAS) consisting of a 100 mm line marked from 0 to 10 (0=no pain, 10=worst imaginable pain) was used to evaluate the efficacy of lidocaine in preventing burning or pain in the nasal cavity due to INM administration. The score was obtained by asking parents during the procedure about their perception of their child's pain. Side effects such as sneezing, coughing, nausea, vomiting, nasal burning sensation or bitter taste were recorded, as were the total dose administered throughout the procedure and the procedure start and end times.

All information regarding drug efficacy, safety, tolerability and procedure times were recorded by an unbiased doctor (fellow) who did not participate in the sedation or in the procedures. The risks, possible discomforts and benefits were explained to the parents and they were required to sign an informed consent form prior to the procedure.

At the end of sedation, the same doctor submitted a questionnaire to the medical staff who did not participate in the sedation but performed the painful procedure, and to the patient's parents (table 2). Physicians and parents indicated on a VAS ('0' for worst, '10' for best) the usefulness of the drug, changes in the child's and parents' outlooks, changes in the child's tolerance of the procedure, changes in the child's behaviour before and during the procedure and whether they would recommend the drug and MAD to other physicians and parents.

Children were discharged 2 h after the administration of lidocaine and INM. One day later, children were re-evaluated either clinically if they were still in hospital or by phoning their parents if they had been discharged, to exclude the occurrence of any side effects. Ethics approval was obtained from the Ethics Committee in our hospital.

STATISTICAL ANALYSIS

Univariate linear regression testing was used to measure the correlation of start time, end time and length of sedation with children's weight and age. Multiple linear regression analysis was performed to obtain adjusted coefficients and to verify any bias between weight and age. A p value <0.05 was considered significant. Coefficient of determination R^2 was taken as a measure of the goodness of fit of the model. Statistical analysis of the data was performed using SPSS v 17.

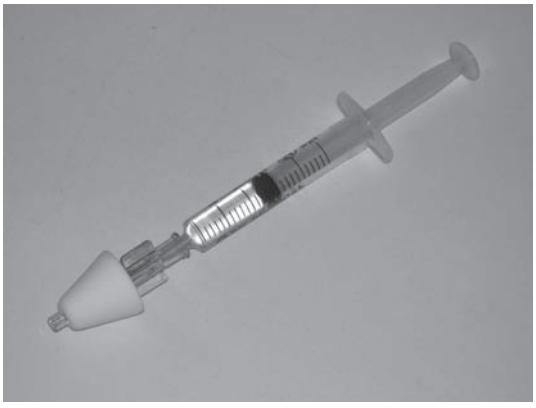

Figure 1 Mucosal atomiser device (MAD) connected to a 2.5 ml syringe.

Table 1 Sedation and reactivity scores

Score	Description
Sedation	
5	Not arousable
4	Arousable if stimulated powerfully
3	Arousable if stimulated moderately
2	Opens eyes spontaneously/on command
1	Patient awake but mildly sedated
0	Not sedated
Reactivity	
4	No reaction
3	Mild reactions that do not disturb the procedure
2	Reactions that disturb the procedure
1	Marked movements that make the procedure impossible
0	Procedure not in progress

RESULTS

Forty-six (22 males, 24 females) children were recruited to the study; their median age was 18 months (range 5–50). All children achieved a healthy ASA classification of 1. Overall, 51 procedures were performed (20 peripheral line placement procedures, 12 venipunctures, 7 intramuscular injections, 5 ECHOs, 4 CT scans, 2 auditory brainstem response tests and 1 dental extraction). No side effects were recorded during the procedures. O_2sat levels ranged between 96% and 100% during sedation. Interestingly, none of the children reported a burning nasal sensation or a bitter taste.

As reported in table 3, the mean time between administering INM and the beginning of the procedure was 6.9 min (SD 2.4 min, range 3–15 min, median 7 min). The mean time between administering INM and the end of the sedation effect was 29 min (SD 11.2 min, range 18–65 min, median 26 min). The mean duration of the sedation effect was 23.1 min (SD 10.35 min, range 10–50 min, median 20 min). A good level of sedation was achieved for all procedures, which was appreciated mainly for peripheral line placement in which only one attempt was necessary in sedated infants. The depth of sedation was 1 on the modified Ramsay scale and reactivity was 3 according to the reactivity score for all children (table 1). Premedication with lidocaine spray prevented any nasal discomfort or pain associated with INM administration, as testified by parents reporting a VAS score below 2 in all children studied. No child required additional drugs or additional INM doses to complete any procedure. Compliance with the full dose was achieved in all 51 procedures, as none of the children refused intranasal administration of the drugs. Patients' mothers reported their appreciation of the ease and utility of this method of drug administration.

All 13 doctors who took part in the painful or diagnostic procedures and all children's parents responded to the questionnaire (table 2),[21] although some did not answer all questions. The median level of appreciation by the medical staff was 8.8. The average level of satisfaction of parents watching the procedures was 9.8. Both parents and medical staff reported a good level of satisfaction regarding the children's behaviour during the procedures (table 2).

A significant correlation of start time was found with age (R=0.57, R^2=0.33; p=0.0002) and weight (R=0.44, R^2=0.20; p=0.0001); multiple linear regression analysis showed a strong correlation only with age (p=0.006) and not with weight (p=0.233). A significant correlation of end time was found with age (R=0.59, R^2=0.35; p=0.0001) and weight (R=0.37, R^2=0.14; p=0.019); multiple linear regression analysis showed a strong relationship only with age (p=0.012) and no correlation with weight (p=0.59). There was no significant correlation between sedation duration and age (R=0.28, R^2=0.079; p=0.085) or weight (R=0.13, R^2=0.017; p=0.43).

DISCUSSION

This study demonstrated that lidocaine spray and INM administered via a MAD are effective when painful procedures and diagnostic investigations in anxious and uncooperative children need to be performed. Previous studies showed that the most common adverse effects after the INM administration were nasal burning and a bitter taste that made sedation with INM difficult.[12–13 18 22–24] In our study, administering lidocaine spray prior to administration of INM, as previously suggested by Lugo *et al*,[18] prevented children from experiencing unpleasant nasal sensations. Based on this experience, lidocaine spray may be used also for preventing nasal discomfort related to other drugs administered by the intranasal route, such as diamorphine recently utilised in the management of acute sickle cell pain.[25] All patients achieved an adequate level of sedation throughout each procedure, without requiring additional drugs or additional doses of midazolam. Moreover, both the medical staff and the parents reported a significant degree of satisfaction with this sedation protocol (see table 2) The association between lidocaine and INM was particularly helpful for peripheral line placement, in which anxiety due to the puncture itself and trouble

Table 2 Parents' and medical doctors' responses to the questionnaire on the administration of intranasal lidocaine and midazolam via a mucosal atomiser device

	Parents (n)	Score (median)	Range	Doctors (n)	Score (median)	Range
Helped	46	10	10–0	13*	10	10–10
Level of child's outlook	42	9.1	8–10	11*	8.5	7–10
Level of parents' outlook	41	8.9	7–10	10*	7.6	6–9
Level of doctors' outlook	–	–		12*	9.2	8–10
Level of child's tolerance of procedures	43	9.3	8–10	12*	9.2	8–10
Judgement on child's behaviour prior to procedure	45	9.8	9–10	10*	7.7	6–9
Judgement on child's behaviour during/after procedure	46	10	10–10	11*	8.5	7–10
Would recommend to other parents	45	9.8	9–10	–	–	
Would recommend to other doctors	–	–		12*	9.2	8–10
Would like to see MAD used routinely	46	10	10–10	12*	9.2	8–10

*13 medical doctors were involved in the painful or diagnostic procedures carried out in the study.
MAD, mucosal atomiser device.

Table 3 Age, weight, start times, end times and duration of the sedation effect in children undergoing procedural sedation by intranasal lidocaine and midazolam

Parameter	Mean	95% CI	Median	95% CI	SD	Minimum	Maximum
Age	26 months	19.1 to 33.2	18 months	16 to 21.9	21.6 months	5 months	50 months
Weight	13.4 kg	11.65 to 15.1	12 kg	10 to 14	8.4 kg	7 kg	18 kg
Start time of sedation effect	6.9 min	6.1 to 7.7	7 min	6 to 8	2.4 min	3 min	15 min
End time of sedation effect	29 min	26.2 to 33.6	26 min	24 to 29.3	11.2 min	18 min	65 min
Duration of sedation effect	23.1 min	19.7 to 26.4	20 min	17 to 23.9	10.3 min	10 min	50 min

finding a suitable vein often make such a procedure difficult in uncooperative infants.[12]

There were no serious side effects, such as oxygen desaturation, bradycardia, hypotension or apnoea, despite the relatively high dose of midazolam used (0.5 mg/kg), confirming that the use of lidocaine and INM is safe, effective and well tolerated by children. In addition, the regression analysis demonstrated that in younger children the onset of the sedative effect of INM is quicker (start time (minutes)=5.1364+0.07336×age). Such variability among different age groups is explained by age related variation in the pharmacodynamics and pharmacokinetics of midazolam due to both genetic polymorphisms and maturation of drug metabolising enzymes.[26–28]

This is the first prospective study using INM with lidocaine premedication, but as it is not a controlled and blinded trial, the results could be biased. In addition, consideration needs to be given to the small number of and different procedures performed. This heterogeneity makes these data difficult to interpret: however, in view of the preliminary results, a multicentre, prospective, controlled, randomised trial would better establish the safety and efficacy of INM in association with local lidocaine for procedural sedation in uncooperative children.

In conclusion, INM administered by MAD could be a simple non-invasive approach for the sedation of children undergoing minor painful procedures or diagnostic investigations. Premedication with lidocaine spray appears to prevent any nasal discomfort, making the sedation more acceptable both for children and their parents. Despite several study limitations, INM administered together with nasal lidocaine has demonstrated a satisfying level of efficacy and no side effects in our series. Further studies are needed to clarify the potential of this protocol for the sedation of children in general paediatric departments and emergency rooms.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee of the Catholic University Medical School of Rome, Italy.

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